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Status of Biomedical Research and Related Technology for Tropical Diseases

Summary

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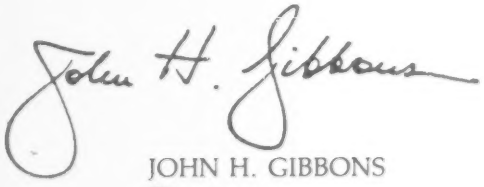
Foreword

Billions of people in less developed areas of the world and a small but growing number of inhabitants of the industrialized countries come into contact with infectious diseases generally characterized as "tropical." Though not necessarily geographically limited, these diseases are most common in the tropics because of the social and economic, as well as climatic, conditions that prevail there.

In combination with the traditional methods of parasitology and basic research, the new tools of biotechnology and immunology have opened doors to finding methods for controlling tropical diseases. Scientists are pursuing technologies for the control of insects that transmit diseases and the development of vaccines, diagnostic technologies, and new therapies for tropical diseases. The potential for making inroads into the overwhelming morbidity and mortality caused by these diseases has never been so great.

The United States continues to make significant contributions toward controlling tropical diseases, but the resources allotted to these efforts are small: in recent years, less than $100 million per year has been spent by the U.S. Government on tropical disease research out of a total annual biomedical research budget of $4 to $5 billion. As one component of U.S. international activities, research in tropical diseases serves several objectives: social and humanitarian, political, economic, medical (including the protection of American citizens), and scientific. Opportunities for expanding U.S. influence and contributions in this field are great.

In the spring of 1983, the Senate Appropriations Committee asked OTA to assess the status of biomedical research and technologies for controlling tropical diseases. An advisory panel, chaired by Dieter Koch-Weser, provided guidance during the assessment. A large number of individuals from academia, the Federal Government, the private sector, and the public provided information and reviewed a draft of the report. Five contractors were essential to the completion of the assessment: Paul F. Basch, Roger A. Bitar, and Veronica Elliott provided information for the body of the report; Myron M. Levine and Lydia Schindler prepared case studies on oral rehydration therapy for diarrheal diseases and on the development of a malaria vaccine, respectively. The final responsibility for the content of the report rests with OTA. Key staff involved in the analysis and writing were Hellen Gelband, Kerry B. Kemp, Susan C. Tripp, and Steven S. Bjorge.



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Status of Biomedical Research and Related Technology for Tropical Diseases

INTRODUCTION

For most of the world's population in less developed countries, mainly in the tropics, good health is not something interrupted by occasional annoying bouts of sickness. One-tenth of the average person's life in a developing country is seriously disrupted by ill health. Life expectancy at birth is nearly 20 years shorter in the developing regions than it is in the developed countries. Each year, millions of infants and children die from enteric and respiratory infections. Several hundred million people are infected with organisms that cause chronic disabling and often life-threatening parasitic diseases: malaria, schistosomiasis, trypanosomiasis, leishmaniasis, and filariasis. **Chronic and debilitating infections with intestinal parasites range, in total, into the billions.**

Researchers in all corners of the globe have aided the efforts against tropical diseases, and the United States has played a major role. Through the work of individual U.S. researchers and institutions and through international collaborations, the United States has contributed to the development of oral rehydration therapy (ORT) for the dehydration that accompanies diarrheal diseases, the rapidly unfolding progress toward development of a genetically engineered malaria vaccine, and other advances in the prevention, diagnosis, and treatment of tropical diseases.

ORT and the malaria vaccine fall at opposite poles of biomedical research and of disease interventions. ORT, developed from research in basic human physiology, has saved the lives of hundreds of thousands of children by treating the lethal dehydration of diarrhea caused by a plethora of organisms. The hope for a malaria vaccine is to prevent at least some part of the 300 million cases that occur worldwide each year. Widespread application of an effective vaccine, still at best 5 to 10 years away, will be dependent on the use of recombinant DNA technology, a tool that did not even exist 20 years ago. These advances are undeniably valuable contributions, both for science and for health. But even these achievements pale in the shadow of the massive health problems that continue to affect the billion or so who live in less developed areas.

This assessment examines the status of control for a selected group of diseases that cause extensive morbidity and mortality in developing countries of the tropics and looks at what the United States is doing in biomedi-

cal research to alleviate the human misery caused by these diseases. **OTA found a great deal of recent progress in tropical disease research and a small, but highly motivated, corps of tropical disease researchers.** OTA also found, however, that the U.S. Government is spending relatively little money on tropical disease research. **The small amount of money spent by the United States on tropical disease research appears to reflect choices in policy, whether implicit or explicit, and not a lack of promising avenues for research.**

Request for the Assessment

The need for an assessment of research in tropical diseases was focused in the spring of 1983, when a question arose about continued U S. funding for Gorgas Memorial Laboratory (GML), a half-century old research institution located in the Republic of Panama. The National Institutes of Health (NIH) requested no funds for GML for fiscal year 1984. If acted upon, the withdrawal of funding would probably have forced the laboratory's closing.

The Senate Appropriations Committee asked OTA to assess the activities of GML and then go on to examine the overall status of U.S.-funded biomedical research for tropical diseases. An OTA technical memorandum fulfilling the first charge, *Quality and Relevance of Research and Related*

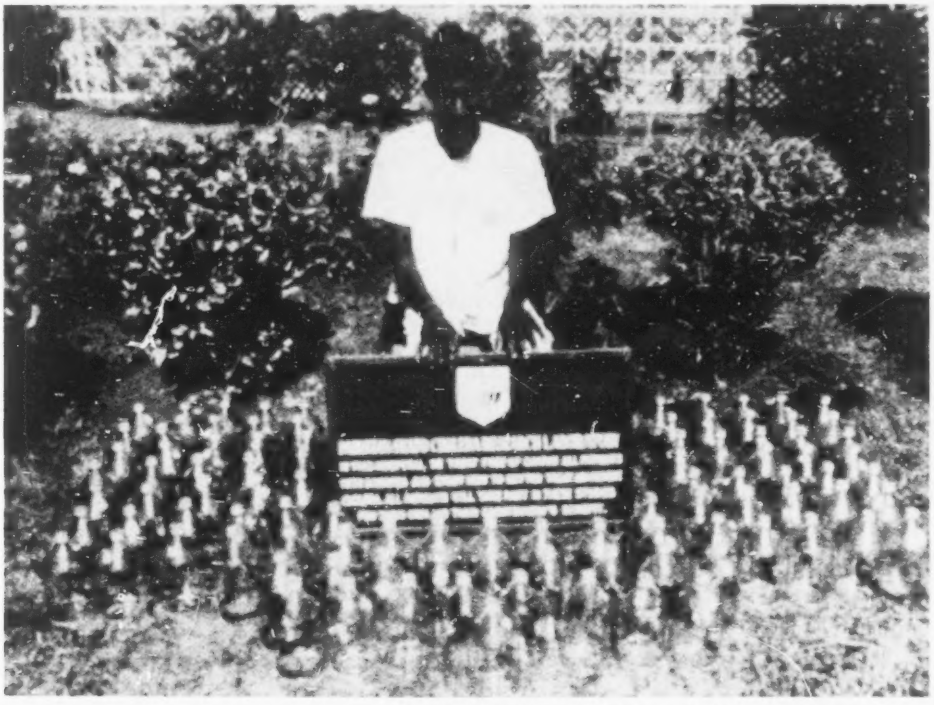

Photo credit: Dr. Robert Edelman, National Institutes of Health

A cholera patient surrounded by bottles that contained the 96 liters of intravenous fluid required for his recovery. Oral rehydration therapy (ORT) has cut the requirement for expensive intravenous fluid by about 75 percent.

Activities at the Gorgas Memorial Laboratory, was released in August 1983. On the basis of that report, a companion report prepared by the General Accounting Office, and other information, Congress restored funding for GML for fiscal year 1984. While recognizing the creditable record of research and service of GML, Congress also required that plans for the future course of the laboratory's efforts take account of some problems identified by OTA and the General Accounting Office.

Scope of the Report

There are many definitions of tropical diseases. In the strictest sense, tropical diseases are those that occur only in tropical areas, between the Tropics of Cancer and Capricorn, and are limited to those areas by geographic and climatic factors. In the broadest sense, they can include any health conditions that occur in the tropics, regardless of their distribution around the world. A more useful definition includes those diseases or conditions that occur or could occur in many regions, but which are considerably more prevalent in tropical areas because of the social, economic, and climatic conditions that characterize many tropical countries.

In this report, no attempt was made to redefine tropical diseases. **For the purpose of this assessment, OTA focused on a limited group of conditions that are unquestionably important causes of morbidity and mortality and that either occur exclusively in the tropics or have greater public health implications in the tropics than in temperate zones.** Included in this group are the six diseases singled out by the Special Program for Research and Training in Tropical Diseases (TDR) of the World Health Organization (WHO)/U.N. Development Program/World Bank: malaria, schistosomiasis, trypanosomiasis, filariasis, leishmaniasis, and leprosy. Also considered in this report are tuberculosis, diarrheal diseases, acute respiratory infections (ARIs), and arboviral and related viral infections.

The focus of this assessment is on biomedical laboratory research pertaining to these diseases and on some field research in the control of insect and other vectors. In general, this report does not address the equally important contributions of entomological research and basic ecological research necessary to improve the understanding of these diseases. It also does not examine research in human behavior and societies or the interactions of humans with the environment, elements that are of great importance in understanding and controlling disease.

BACKGROUND ON TROPICAL DISEASES

Health in the Tropics

In many developing countries of Africa, Asia, Latin America, and other parts of the world, infectious diseases, which have been eliminated as major causes of death in the United States and other developed countries, are the biggest killers. The victims are often infants and children. In the United States, only about 11 of every 1,000 live born babies die in the first year

of life, and many of the deaths are attributable to problems evident at birth—low birthweight, premature birth, birth defects, and respiratory problems, for example. In the developing world, as many as 200 of every 1,000 babies born die before their first birthday. The causes are almost entirely infectious diseases—especially diarrheal diseases, ARIs, and malaria. In Latin America and the Caribbean, diarrheal diseases are the leading cause of death in children under 5 years of age. **Worldwide, as many *children* die from diarrheal disease, as there are *total* deaths from cancer.** In many places where diarrheal diseases are under better control, ARIs are the main cause of death in children. Although ARIs are common among children in the United States, they rarely are fatal, causing a total of about 5,000 deaths per year (not including influenza).

People in the less developed countries of the tropics are not only afflicted with diseases that seldom occur in temperate regions—e.g., malaria, schistosomiasis, trypanosomiasis, leishmaniasis, and filariasis; they are also afflicted with the diseases of the developed countries in temperate regions. In fact, some types of cancers are more common in less developed countries than they are in the United States or Europe. Certain areas of Central America have the highest known rates of cervical cancer in the world. Parts of Africa and Asia have extremely high rates of liver cancer. Heart disease has become more common in less developed countries as well, particularly in urban areas. Sexually transmitted diseases are more prevalent in many developing countries than they are in the United States.

The presence or absence of good health is determined by forces that interact with the effects of particular agents of disease. Poor nutrition, high birth rates, and lack of education, especially for women, are conditions that exist in the less developed countries with the poorest health. Poverty itself, if defined in terms of per capita income, does not necessarily condemn a country to ill health. In Cuba, for instance, where the average salary is about $200 per month, there has been great emphasis since the 1959 revolution on providing universal access to health care, providing for adequate nutrition, and providing for universal education. Life expectancy in Cuba is now close to that in the United States. The infant mortality rate has been cut from over 100 per 1,000 before the revolution to about 17 per 1,000. Malaria and diphtheria have been eliminated from Cuba. Deaths from diarrheal diseases and tuberculosis, formerly important public health problems, are negligible.

In many less developed countries, however, malnutrition is a primary factor in disease. Poorly nourished people are more susceptible to disease and often suffer more severe effects when they contract disease. Where the case fatality rate from measles is high, the deaths are generally of undernourished children. The body's immune system and recuperative powers both are diminished by the lack of adequate nutrition. Undernourished pregnant women are of special concern. The babies born to such women are often of low birthweight, which is the main predictor of infant mortality. Those that survive past infancy may themselves be weak and prone

to infection. The mothers may be unable to produce sufficient milk to nourish the infants, perpetuating the cycle of undernourishment.

Many scientists believe that the high infant mortality rates associated with undernutrition lead to high birth rates. Families who depend on children as workers and for support in old age attempt to have enough babies to ensure the survival of a few. As women undergo pregnancy after pregnancy, they become progressively weaker themselves and have fewer resources for the surviving children. The last children born to them may be the weakest, and most prone to die in infancy or childhood.

Educating women is an important step toward better health. Educated women are better able to learn about the role of nutrition in their own and their children's health and may improve the probability of their children's survival. Though cause and effect would be hard to prove, for each year of schooling for women, the World Bank has estimated that the infant mortality rate is reduced by nearly 1 percent. Education also leads to higher expectations for the women and for their children, which promote better health.

The cycle of malnutrition, disease, and high birth rates can be broken in a number of ways. This report focuses on technologies to address the problems of disease directly. A 1982 OTA report considered current and developing technologies for world population and fertility planning. A more recent OTA study addressed technological alternatives to food aid in Africa.

Tropical Diseases in the United States

Although some "tropical diseases" are in large part restricted to the tropics because the conditions necessary for their existence have been limited by geography or climate, many "tropical diseases" are not limited by natural factors to the tropics, but also occur in temperate areas, including the temperate United States. The semitropical and tropical areas of the United States are, of course, vulnerable as well.

Diarrheal diseases and ARIs occur in all parts of the world. In the United States, virtually all children survive bouts of diarrhea and colds with little or no long-term consequences. What makes diarrheal illnesses and ARIs important as "tropical diseases" is the fact that infants and children in developing countries commonly die from them.

Tuberculosis was among the leading causes of death in the United States early in this century. Improved living conditions for most Americans decreased transmission of the disease to fairly low levels. Tuberculosis still is widespread in the developing world and wherever substandard, overcrowded living conditions exist. In 1982, more than 25,000 U.S. cases, undoubtedly an underreporting, were registered by the Centers for Disease Control (CDC). Tuberculosis is common in the home countries of many recent refugees coming to the United States. In 1982, at least 300 refugees entered the United States with active tuberculosis.

Malaria was endemic to the United States until its elimination in about 1950, but the conditions for its reestablishment in some parts of the country still exist. In 1982, a total of 1,056 cases of malaria in the United States were reported to CDC, fewer than the previous 2 years. All but 17 cases were acquired outside the United States. The 17 cases acquired in the United States were either congenital, associated with blood transfusions, or accidentally acquired in the laboratory. Very recent evidence suggests that malaria caused by *Plasmodium vivax* is being transmitted among farmworkers by mosquitoes in the central valley of California.

Chagas' disease (American trypanosomiasis) has been limited to the New World tropics and never was endemic to the United States. However, the insect vectors of Chagas' disease (reduviid bugs) are present across the Southern United States, and at least some are infected with trypanosomes. A case of Chagas' disease transmitted by an insect in northern California was diagnosed in 1982, the first such case reported in the United States since 1955, when two infants in Texas were diagnosed with domestically acquired Chagas' disease.

Four cases of leishmaniasis transmitted in the United States were reported at the 1983 annual meeting of the American Public Health Association.

Some of the traditionally tropical arboviruses are extending their ranges within the tropics and to temperate areas, probably aided by the increase in air travel over the past decade. The principal vector of dengue fever and yellow fever, the mosquito *Aedes aegypti*, is common throughout the world, including the Southern United States. In 1982, there were 45 cases of dengue fever confirmed by CDC, in 14 States. Since 1977, 855 suspected cases have been reported, some from almost all the States. Epidemiologic investigations have indicated that most of the infections were contracted outside the United States. More significant though, are the approximately 40 cases of dengue fever contracted in the United States in 1980, the first such reports since 1945. Venezuelan equine encephalitis has been recently introduced into the United States from South America. In other parts of the world, arboviruses, including those that cause Rift Valley fever and African swine fever, also have demonstrated their ability to spread.

Leprosy is transmitted in this country. Since 1970, somewhat fewer than 30 cases have been acquired domestically each year. The total number of cases reported annually in the United States has been increasing, however, because of an increase in cases acquired outside the country. A sharp increase in the number of leprosy cases since the mid-1970s corresponds to the pattern of refugees entering the United States from Southeast Asia.

There are a number of ways for "tropical diseases" to become established or reestablished in the United States. Such diseases could be spread into the United States gradually from contiguous geographic areas (e.g., from Latin America through Mexico). They also could be introduced from endemic areas by Americans who have contracted diseases abroad or by foreign visitors or immigrants entering the country. Between fiscal year 1975 and 1982, more than 800,000 refugees, most from Asian areas where tropical diseases are prevalent, entered the United States and have since settled

in all parts of the country. A large number of other immigrants also come from tropical areas.

The United States has a relatively strong system of disease surveillance that allows the detection of unusual disease activity in the country and near U.S. borders. However, **the scientific basis for predicting whether a disease is likely to become established or reestablished is fairly weak.**

Climatic conditions do not favor the establishment of some diseases in the United States, and for other diseases (e.g., African sleeping sickness) suitable vectors (tsetse flies in the case of sleeping sickness) are absent, although for most vector-borne diseases, little is known about the capacity for alternate insects to become vectors.

U.S. Citizens at Risk for Tropical Diseases

The risks of contracting tropical diseases in the United States, either from infected individuals or from insects transmitting disease, are compounded for Americans who travel to other countries.

The longstanding interest of the U.S. Department of Defense (DOD) in tropical diseases has practical roots. It is said that during World War II more U.S. troops in the Philippines were hospitalized with malaria than were hospitalized with injuries of war. The same was true of our troops in Vietnam. Currently, more than half a million American military personnel are abroad, many located in the tropics.

In addition to military personnel, substantial numbers of Americans reside in less developed countries as employees of U.S. and international aid and development agencies or of multinational corporations. An even greater number annually travel to the tropics, no longer so far off and inaccessible as they once were. **In all, about 5 million Americans each year are at risk of contracting a tropical disease.**

APPROACHES TO CONTROLLING TROPICAL DISEASES

The goal of most tropical health programs is control of disease. In this report, the term control refers to the reduction of morbidity and mortality from disease using any or all of the spectrum of biomedical and environmental tools. Control is not synonymous with eradication, because eradication implies permanent elimination of a disease from the face of the earth. **While the possibility exists that certain tropical diseases can be eradicated following the example of the spectacular success with smallpox, most of these diseases cannot be either because of biological or practical constraints.** Many tropical diseases can be *eliminated* from geographic areas, while existing in other parts of the world. The control of others can be achieved by maintaining low levels of incidence and prevalence.

Providing clean water and sanitation systems, coupled with education and behavioral changes, removes the sources of infection and the means of transmission for many diseases that are rife in developing countries. In the United States, at least since 1900, long before the antibiotic era, the

spread of public works, particularly sanitation measures, was leading the country out of the thrall of infectious diseases. As Lewis Thomas has said, "Much of the credit [for improved health] should go to the plumbers and engineers of the Western World."

The development of more specific disease control measures is heavily dependent on basic and applied biomedical research. The probability that researchers will develop successful control measures for tropical diseases has never been greater than it is today.

The advent and explosive growth in the use of "biotechnology"—recombinant DNA techniques and other sophisticated tools relying on the ability to harness and manipulate genetic material—have given a boost to the study of tropical diseases. Using methods formerly unavailable, immunologists and molecular biologists are beginning to understand the unique biology of the parasitic organisms that cause malaria, schistosomiasis, trypanosomiasis, filariasis, and leishmaniasis. This progress has led to vaccine research and to a new generation of badly needed diagnostic tools for parasitic diseases, as well as bacterial and viral diseases.

Although there is obviously great progress in controlling tropical diseases to be made through the use of biotechnology, there remains a need to continue more traditional research approaches in parasitology, infectious disease natural history, and basic biomedicine. This need is particularly acute for tropical diseases, because these diseases are much less well understood than diseases of importance in the United States. Such basic information about tropical diseases as the ranges of insect vectors that transmit many of them, their natural history, and their prevalence is incomplete. Although control of one or a few of these diseases is conceivable without such information, for most of the diseases, such information will be required before adequate control measures—which will of necessity integrate aspects of vector control, prevention, diagnosis, and treatment—can be designed.

The control of mosquitoes and other vectors (where appropriate) has been a successful route of disease control in certain geographic areas for several diseases. The elimination of malaria in the United States, in most of Europe, the Caribbean islands (except for Haiti and parts of the Dominican Republic) and other parts of Latin America was accomplished, at least in part, through control of the mosquitoes that transmit the disease. Similarly, through control of mosquito vectors, yellow fever was eliminated from Panama at the turn of the century, allowing completion of the Panama Canal.

Before the use of DDT (dichloro-diphenyl-trichloroethane) in the 1940s, vector control programs were based largely on physical measures, particularly on removing standing water where larvae could develop. In Africa, early control programs for tsetse flies, the vectors of African sleeping sickness in humans and nagana in livestock, relied on geographic isolation of flies (one strategy involved burning swathes of vegetation to prevent migration) and efforts to kill large numbers of flies manually. Although some schemes were more successful than others, the tsetse control efforts on the

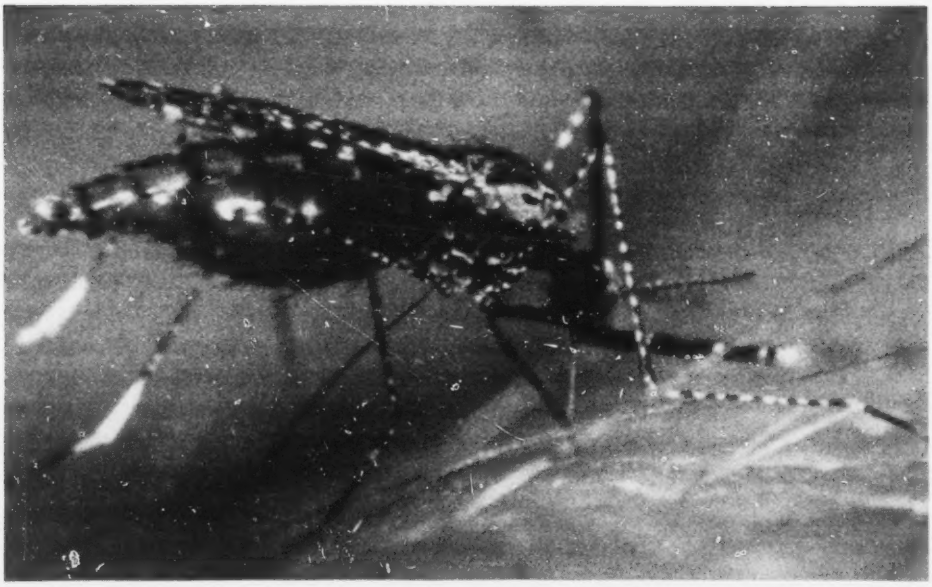

Photo credit: Robert Edelman, National Institutes of Health

Anopheline mosquito, which can transmit malaria to humans, after a blood meal.

whole, failed, at least in part because of a lack of effective coordination among a number of African nations.

After the advent of DDT, hope for controlling and eradicating diseases focused on chemical pesticides. The "malaria eradication program," announced in the mid-1950s, was WHO's first global initiative. WHO's promotion of a malaria eradication campaign was based on what is perceived in retrospect as the overly optimistic hope that a single intervention by insecticide could be effective. An appreciation of the ability of insect vectors to develop resistance to pesticides and of the complexity of interactions among vectors, humans, and the environment was the lesson learned from WHO's unsuccessful efforts. **Pesticides, even DDT, still have a place in strategies for disease control, but no single technology is likely to be able to control most vectors of disease**. The integration of chemical and biological approaches in "integrated pest management" (IPM) may provide the long-term solution, though as yet successes are few in this rather new field.

The application of biotechnology and immunologic tools has yielded a great deal of information about the biology of disease vectors. Specific arthropod vectors once thought to be homogeneous single species are now known to be "species complexes." Different species complexes may vary subtly or dramatically in their behavior and susceptibility to the organisms that cause disease. While appearing identical, their roles as disease vectors may be distinct as well. Knowledge about the vectors that transmit certain tropical diseases may become the basis for designing rational control programs.

As a technology, vaccination to prevent disease has had the greatest impact on health to date and still holds enormous potential. The principle of vaccination—the stimulation of the body's ability to fight off pathogens before they can cause disease—was established long before the germ theory of disease was developed. As early as 500 years ago, it was common practice in India, China, and probably Africa to scratch a bit of material from smallpox pustules into the skin of healthy people. The result of this process, called variolation, was to provoke a mild case of disease and thus render the person immune to further infection. Today's familiar vaccines—measles, rubella, mumps, diphtheria, whooping cough, tetanus, and yellow fever, for example—have been developed through one of several "conventional" methods. The pathogenic organism itself (attenuated or inactivated) or part of the organism is deliberately introduced into the body to prime the immune system to combat future infections.

Vaccine development has moved into a new era with biotechnology. Scientists' ability to decipher genetic codes and pinpoint the proteins that trigger an immune response has opened the door for subunit vaccines that may be safer and more specific than those derived from whole or partial disease organisms themselves. The first genetically engineered human vaccine, for hepatitis B, is now in early immunogenicity trials in humans. Progress toward a malaria vaccine puts initial trials in humans perhaps as early as 1986, but development of the vaccine for general use is probably 5 to 10 years off if no major problems occur.

Besides the development of the vaccines themselves, the mode of vaccine delivery occupies the attention of biomedical researchers and engineers. The "bifurcated needle," nothing more than a double-pronged needle which holds one drop of vaccine between the prongs, is one of the technologies credited with making smallpox eradication possible. The various vaccination devices used previously were, for a variety of reasons, not as well suited to the needs of the worldwide smallpox campaign. The bifurcated needle was developed by industry in response to the needs of the campaign, which was already under way.

Trials of "aerosolized vaccines," which are inhaled, have been going on for the past 10 years. Just last year, in 1984, Albert Sabin, the oral polio vaccine pioneer, reported successful measles immunization using an aerosolized vaccine. Delivered in an aerosol form, the vaccine was more effective than it had been when given by injection. This technique may prove important for a wide range of ARIs.

Just as important as vaccination devices in the tropics are technologies for the mass production, storage, preservation, and distribution of vaccines. Concerns about these functions relate to the stage of development of organized health services as well as to medical technologies per se. One of the most critical needs for immunization programs involving certain vaccines, for instance, is the maintenance of a "cold chain," the means to keep vaccines cool during transportation from the laboratory to the vaccinee, wherever that person might be.

Photo credit: Dr. Stanley O. Foster, Centers for Disease Control

Vaccination against smallpox using a bifurcated needle.

Lack of adequate diagnostic technologies has hampered the study and treatment of many tropical diseases. In addition to benefiting individual patients, diagnostics are needed to learn about the ranges of diseases and their prevalence and incidence. **Although there is a wide range of conventional diagnostic tests that are adequate for some tropical diseases, the need for rapid tests that do not require sophisticated laboratory equipment remains.**

Biotechnology has made significant contributions in diagnostics. As a result, rapid diagnostic tests, which can be used under field conditions, are now under development. Diagnostic capability based on the DNA of the disease organisms has also brought to light within-species differences in disease organisms. Although the differences are subtle, they may eventually have significance for controlling diseases.

Research and development in therapeutic technologies for tropical diseases have lagged behind research and development in technologies for diseases of U.S. importance. **Few new drugs have been introduced for human tropical diseases in the past two decades, though there has been a surge in the development of products for parasitic infections of domestic animals. One reason why pharmaceutical companies have been reluctant to invest heavily in drugs for tropical diseases is that many of the potential beneficiaries of drugs cannot afford to buy them.** While a company may produce an effective drug, there may be no market for it.

Notwithstanding the general slow progress in the development of therapeutics for tropical diseases, there have also been some new and exciting developments.

The discovery in the 1960s that glucose is actively transported in water into the body through the intestinal wall even during severe diarrhea paved the way for the development of ORT. ORT is a major therapeutic measure for diarrheal dehydration that has the potential to significantly alter the mortality statistics of developing countries today. It is not a pharmaceutical in the usual sense, nor is it even a curative agent. ORT is a nonspecific treatment for episodes of diarrhea, particularly prevalent among children, and responsible for at least one-third of all infant deaths in developing countries.

ORT was developed as a treatment for cholera, first in adults, then in children and infants. Its efficacy for a wide spectrum of diarrheal diseases has since been proved. Increasingly, less developed countries are undertaking national diarrheal disease control programs in which ORT constitutes the keystone of the program. WHO and the U.S. Agency for International Development (AID) both are supporting major programs in ORT.

Praziquantel, a drug marketed in 1980, has revolutionized the treatment of schistosomiasis. Previously, schistosomiasis treatment itself involved major health risks, and was a long process. Praziquantel has overcome both of these problems and would probably replace the previous drugs of choice (which have disadvantages) if it were not so expensive.

Several new drugs for prophylaxis and treatment of malaria have been introduced in the past decade. The development and spread of malaria parasites resistant to chloroquine, for many years the drug of choice, has made the quest for new antimalarial drugs imperative.

Activity against a tropical disease by an antiviral drug, ribavirin, has been demonstrated for the first time. This broad spectrum antiviral was shown to be effective against Lassa fever in animals by researchers at DOD. CDC scientists took ribavirin to the field in west Africa, where Lassa fever is a major problem, and the drug proved effective in humans.

STATUS OF CONTROL FOR SELECTED TROPICAL DISEASES

Control measures for tropical diseases vary in their availability, safety, and effectiveness. The status of preventive, diagnostic, and therapeutic technologies for the diseases considered in this assessment is summarized below.

Malaria

Malaria is one of the most widespread diseases in the world. In the last decade, its world prevalence has increased more than twofold. Worldwide, an estimated 250 to 300 million cases occur each year. In tropical Africa alone, an estimated 160 to 200 million people are infected every year, and 1 million people die, mostly infants and children. Human malaria is caused by four species of protozoan blood parasites of the genus *Plasmodium*. Different species are important in different parts of the world, although there is some overlap. The parasites have a complex life cycle and are transmitted to humans by mosquito vectors of the genus *Anopheles*.

The tools now available to control the mosquitoes that transmit malaria are inadequate to the task. Varying degrees of resistance have been developed by the mosquitoes to every insecticide that has been tried, and there is no reason to hope that a new conventional insecticide will be more successful on a long-term basis. Work on biological control methods (e.g., the introduction of mosquito predators) is needed.

Another problem in malaria control is the spread of strains of malaria parasites that are resistant to chloroquine and other antimalarial drugs. Screening and testing of new compounds has proceeded at a steady pace since about World War II, however, and a few of new drugs are now in various stages of development and testing.

The most exciting development in malaria control is the prospect of a vaccine. Advances in biotechnology have made hopes for a vaccine realistic. With continued success, optimistic estimates put a malaria vaccine on the market in 5 to 10 years.

Schistosomiasis

Schistosomiasis is a chronic, debilitating, parasitic disease caused by trematode worms of the genus *Schistosoma* that live in vertebrate host blood vessels. The three major species of schistosomes that affect humans (*S. mansoni, S. haematobium,* and *S. japonicum*) have a complex life cycle, requiring certain freshwater snails as intermediate hosts. These parasites together have a pantropical distribution. A 1972 survey including 71 countries estimated that 500 million people were exposed to schistosomiasis and 125 million were infected.

In recent years, there has been a drop in the incidence and prevalence of schistosomiasis in some areas and an increase in others. Preventing transmission of schistosomiasis is accomplished most effectively by reducing human contact with infected water. Piped water supplies and excreta disposal are therefore the most effective control measures. Molluscicides (agents for killing snails) are available, but all have adverse environmental side effects and do not provide a permanent solution to control. Biological methods to control snails are under investigation.

In some areas, large-scale hydroelectric and agricultural irrigation projects have been responsible for spreading schistosomiasis by providing year-round breeding sites for snails. The best known case is the Aswan High Dam in Egypt. According to a 1937 survey, about 5 percent of the population in

Photo credit: Dr. Robert Edelman, National Institutes of Health

Many people in tropical countries, particularly children, contract schistosomiasis from irrigation canals that harbor snails in which the disease parasites develop.

upper and middle Egypt was infected with schistosomiasis. Following the construction of the Aswan High Dam, the prevalence rate rose to 30 percent. Areas where large-scale development projects are undertaken may require special surveillance and control measures to prevent human health problems.

Chemotherapy for schistosomiasis, using Praziquantel, along with previously available drugs, is effective and relatively safe. Work on a schistosomiasis vaccine is still in exploratory stages.

Trypanosomiasis

Trypanosomiasis is a group of clinically different diseases of the blood and tissues caused by different species of the genus *Trypanosoma*. The important human diseases are African sleeping sickness and Chagas' disease.

African Sleeping Sickness (African Trypanosomiasis)

African sleeping sickness is caused by two varieties of *Trypanosoma brucei*, which are transmitted by different species of tsetse flies (genus *Glossina*). In west Africa, the disease is caused by *T. b. gambiense*, while in east Africa, it is caused by *T. b. rhodesiense*. *T. b. gambiense* causes a chronic, debilitating disease in humans that saps the energy and eventually kills. *T. b. rhodesiense* infects both humans and animals. People become infected when they enter hunting grounds and grazing areas where there are infected animals. The disease is rapidly fatal to humans and destructive to domestic livestock.

Control of tsetse fly vectors of sleeping sickness has, by and large, been unsuccessful. Consequently, large areas of land have been abandoned or left unsettled because of the threat of disease.

Therapy for African sleeping sickness requires hospitalization because of the use of toxic, intravenously administered, and frequently only partially effective drugs over an extended period of time. Safe, effective, short course chemotherapy is needed.

Chagas' Disease (American Trypanosomiasis)

Chagas' disease occurs in almost every country of Latin America. The disease is caused by *Trypanosoma cruzi*, a protozoan parasite that lives in the blood and tissues. It is transmitted to humans and about 150 other species of mammals by reduviid bugs, blood-sucking insects found throughout the Americas. Reduviid bugs are harbored in the mud and thatch of substandard housing, and the transmission of Chagas' disease is especially high in rural areas. In 1974, WHO estimated that out of 50 million exposed, 12 million people were infected with *T. cruzi*.

The acute phase of Chagas' disease, which may cause heart and nervous system damage, can be fatal, but it usually passes into a chronic stage. Heart failure and grotesque enlargement of the digestive tract are among the long-term sequelae which lead to death.

There is no effective treatment beyond the acute phase and no vaccine. Control measures for Chagas' disease concentrate on periodic insecticide spraying of houses. Improved house construction, which could eliminate breeding sites for aduviid bugs, could provide a permanent control solution.

Leishmaniasis

Leishmaniasis is the collective term for a spectrum of parasitic diseases caused by several species of the protozoan genus *Leishmania*. All species, which segregate largely into Old World and New World forms, are transmitted by blood-sucking phlebotomine sandflies. In 1977, an estimated 400,000 new cases of leishmaniasis occurred worldwide, and in some countries, the number is increasing. Many wild animals in jungle areas that are being cleared for agricultural development are infected with leishmanial parasites, putting new settlers at risk.

Depending on the infecting species, leishmaniasis takes several clinical forms. In the least severe form, cutaneous leishmaniasis, self-resolving skin lesions appear at the site of the insect bite. In the mucocutaneous form, sores may spread into the nasal and pharyngeal mucous membranes, disfiguring the face, nose, and throat. The most destructive form, called "kala azar," attacks internal organs—spleen, liver, bone marrow, and lymph glands—and in epidemics kills thousands of people. Recent epidemics in Asia have resulted from reemergence of the sandfly vectors after spray programs were discontinued.

There is no vaccine against leishmaniasis. Therapeutic drugs for treating leishmaniasis, mainly antimony compounds, are not always effective and have serious side effects. Rapid field diagnostic techniques are being developed through biotechnology. These techniques could both help patients by detecting disease earlier in its course and facilitate field epidemiologic studies of the natural history of the disease. Overall, control of leishmaniasis is poor.

Filariasis

At least eight species, in several genera, of filarial nematode worms, threadlike in form, inhabit the skin, other tissues, or the lymphatic system, causing filariasis in humans. These parasites are transmitted by blood-sucking insects.

Of the many filarial worms that infect humans, three are of major public health importance on a global scale: *Wuchereria bancrofti* and *Brugia malayi*, both of which can result in elephantiasis; and *Onchocerca volvulus*, which is the agent of onchocerciasis (river blindness). *W. bancrofti* and *O. volvulus* are widespread in Africa, and *B. malayi* in parts of Southeast Asia. All three of these species have become established to lesser degrees in the New World.

There are no vaccines to prevent filariasis. Treatment for all forms of filariasis is similar. There is effective therapy for the microfilariae that cause the symptoms of disease, but no nontoxic therapy against adult worms.

All available drugs have side effects, some serious. There is a great need for improved filaricidal agents and immunopotentiating agents, drugs able to stimulate the natural defenses of the body.

Leprosy (Hansen's Disease)

Worldwide, an estimated 15 million people have leprosy, most of them in the Old World. The disease ranges from "tuberculoid" leprosy, with localized skin lesions and minor nerve involvement, to the severe "lepromatous" leprosy, with spreading, disfiguring lesions, resulting in destruction of the nose, involvement of the vocal cords and eyes, and severe nerve damage.

The agent that causes leprosy, *Mycobacterium leprae*, is closely related to the bacterium that causes tuberculosis. Although leprosy has been recognized and feared for centuries, frustratingly little is known of its natural history. Even the way in which leprosy is transmitted is not clear. The most likely means is through the respiratory tract, infection being acquired by direct contact with infected individuals.

Treatment of leprosy involves months or years to a lifetime of treatment with a combination of drugs. There are only a handful of useful drugs, most of which do not actually kill the bacteria, but only arrest its spread. Resistance has developed even to the most effective drug. Considerable progress has been made toward a leprosy vaccine, but it is difficult to predict whether a vaccine will be successful as a control measure for the majority of those at risk. Technical problems in studying leprosy, particularly scientists' limited ability to culture *M. leprae* in the laboratory, have hampered research in all areas of leprosy control.

Tuberculosis

Tuberculosis is a major public health problem in most developing countries and is a resurgent problem in some crowded, poor inner cities in the United States. It is also the most common serious infectious disease among Indochinese refugees to the United States. Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis* and is transmitted from person to person by airborne droplets. The lungs are infected first, but infection can subsequently spread to all parts of the body. Infections are chronic and debilitating if untreated.

The vaccine against tuberculosis is known as BCG (Bacillus Calmette-Guerin) vaccine. BCG vaccine is used mainly in areas of high transmission rates, but its effectiveness has shown great variability in field trials in different parts of the world. There is adequate treatment now for most cases of tuberculosis, though there are drug-resistant strains. A minimum of 6 to 9 months treatment is necessary with the best drugs in combination. In many tropical countries that use less expensive and less effective drugs, much longer treatment is necessary. New antibacterial agents are needed.

Diarrheal and Enteric Diseases

Diarrheal diseases occur throughout the world. Research since the early 1970s has uncovered an array of organisms that cause diarrheal diseases, and there is a continuing need to identify and characterize these organisms. The agents of diarrheal diseases include viruses, bacteria, and protozoa. These agents are transmitted to humans by fecal contamination of food or water.

The greatest danger in diarrheal disease, regardless of the specific cause, is severe, life-threatening dehydration and shock. In adults, diarrheal diseases other than cholera are generally not life-threatening. In children under 5 in many developing countries, however, diarrheal diseases are the leading cause of illness and death. Infants and young children in developing countries may experience four to eight separate episodes of diarrhea per year. One out of every 150 to 200 episodes results in severe, life-threatening dehydration.

One way to prevent diarrheal diseases is to break the transmission cycle by providing clean water and sewage disposal. The encouragement of breast feeding, proper weaning practices, and health education could also help. Vaccines against rotaviruses, *Shigella*, and *Salmonella*, the agents of a large percentage of childhood diarrhea, are undergoing development.

From World War II through the 1970s, the only accepted means of treating diarrheal dehydration was through intravenous replacement of body water and salts. In the late 1960s and continuing into the 1970s, a therapy for diarrheal dehydration was developed that has been called the most important therapeutic advance in tropical medicine. That therapy, ORT, involves the oral administration of a simple solution of water, salt, and sugar and thus does not require hospital facilities. ORT has revolutionized the treatment of adults with cholera and, even more importantly, is effective in infants and children with a wide range of diarrheal infections.

Acute Respiratory Infections (ARIs)

ARIs are among the most important causes of preventable deaths in the world. These infections include both lower respiratory tract infections (e.g., pneumonia and bronchitis) and upper respiratory tract infections (e.g., influenza, measles, diphtheria, and whooping cough). The organisms that cause ARIs are transmitted by airborne droplets and include viruses, bacteria, and mycoplasma.

In developed countries, the toll from ARIs (other than influenza in pandemic years) is relatively low and stable. ARIs are exacerbated by malnutrition and substandard living conditions, however, and in developing countries, these infections take a large annual toll. Some 12 percent of all deaths of children living in Africa, Central America, and Asia are attributed to ARIs. ARIs not only pose a serious mortality risk for the very young and very old in developing countries, but reduce productivity in all age groups and impose tremendous demands on health care systems.

Effective vaccines are available for measles, pertussis (whooping cough), and diphtheria, but a large percentage of the world's children have not been vaccinated. Immunization rates have increased in some countries as a result of WHO's Expanded Program on Immunization (EPI), but EPI's goal of universal vaccination of all children is still far from being realized. Vaccines for pneumococcal pneumonia and influenza are available, but have limited use in developing countries.

The lack of adequate rapid diagnostic methods that can be used in less developed areas of the world hampers effective treatment of ARIs. Some researchers are attempting to develop new diagnostics with the methods of biotechnology. Effective treatments exist for many of the bacterial and mycoplasmal ARIs, but the development of antiviral chemotherapy is still in its infancy. For bacterial ARIs, resistance to penicillin and other antimicrobials is an increasing problem.

Arboviral and Related Viral Infections

The name "arbovirus" is derived from the descriptor "arthropod-borne virus." The unifying characteristic of arboviruses is that they replicate in and are transmitted by arthropods (predominantly mosquitoes, but also ticks, sandflies, midges, and gnats). Arboviruses occur worldwide, infecting humans and other animals. The 80 or so human types have varying distributions and exhibit an apparent trend toward spread rather than containment. Many of the viruses that principally infect animal populations also cause occasional severe outbreaks in human populations.

Important arboviral infections in terms of severity and prevalence are yellow fever, dengue fever, oropouche fever, chikungunya, Japanese encephalitis, other viral encephalitides, and hemorrhagic fevers. Clinically, arbovirus infection can cause either mild disease (e.g., acute benign fevers or self-limiting arthritic symptoms), severe central nervous system disease with brain inflammation which can be fatal, or hemorrhagic fevers with high case-fatality rates. Yellow fever also causes liver damage and jaundice.

Effective vaccines exist for yellow fever and Japanese encephalitis, and work is proceeding on vaccines for dengue fever and a few others. Vector control, at present, provides the most promising avenue for control. Development of therapeutic drugs for arboviral infections is still in its infancy. Treatment for such infections now consists mainly of relieving symptoms.

U.S. EFFORTS IN TROPICAL DISEASE RESEARCH

Rationale for U.S. Efforts in Tropical Disease Research

The reasons for U.S. involvement in tropical disease research, and in the whole area of international health, have not changed since the end of World War II. It was at that time that the United States began to provide substantial amounts of aid to encourage the development of less developed nations. The Interdepartmental Committee on International Health Policy, a group set up in 1960 as one attempt at coordination among the interested agencies,

identified four basic objectives of international health policy. Restated here, they are:

1. **Social and humanitarian objectives.** The ideals and the humanitarian and philosophical beliefs basic to the American democratic tradition should be reflected in U.S. international health activities. The desire for the world's people to enjoy good health is an extension of the attitude of Americans toward their own health.
2. **Political objectives.** Involvement in international health contributes to the U.S. position of world leadership. The United States is not alone in supplying aid in international health. In addition to European nations, Cuba, for instance, is extremely active, with health personnel now in about 25 countries. Health programs can contribute to the political stability of developing nations.
3. **Economic objectives.** Improved health in developing countries can have economic benefits for those countries as well as for the United States. For the countries themselves, increased productivity can accompany gains in health. For the United States, markets for U.S. goods and the atmosphere for U.S. investments may improve with increased involvement in the health sector.
4. **Medical objectives, including self-protection against diseases.** The self-interest of protecting Americans from tropical diseases is increasing in importance as the world community grows smaller. Americans abroad, as well as at home, may be exposed to the risks of tropical diseases. In addition, there may be spinoffs in understanding or controlling diseases of importance in the United States. For example, techniques developed during the campaign against smallpox have been successfully applied to measles control in this country.

To these four may be added a fifth objective:

5. **Scientific objectives.** Tropical diseases pose challenging problems for scientists who are interested in advancing knowledge and improving health.

U.S. Activities in Tropical Disease Research

The major U.S. Government supporters of tropical disease research are: the National Institutes of Health (NIH), mainly the National Institute of Allergy and Infectious Diseases (NIAID), and CDC (both in the U.S. Department of Health and Human Services); DOD; and AID. Each U.S. Government agency supporting tropical disease research acts in accordance with its own specific mandates, which by and large do not overlap with the mandates of other agencies. NIH funds research of scientific merit that will advance the state of knowledge about causative agents, the response of humans to the disease agent, and the disease itself. CDC responds to specific problems around the world in the control of diseases as they affect the health of U.S. citizens, and also maintains applied research programs in diseases of public health concern (e.g., malaria and helminthic diseases). DOD focuses on health problems of direct relevance to U.S. military per-

sonnel in different parts of the world. Most AID-funded research has relevance to development assistance and political objectives.

The Federal agencies that fund research do so under various legislative mandates, which for the most part allow, but do not necessarily encourage, delving into tropical health issues.

The U.S. Government also contributes to research through programs supported by WHO and through TDR (the Special Program for Research and Training in Tropical Diseases), which is administered by WHO, cosponsored by WHO, the U.N. Development Program and the World Bank, and funded by international contributions).

Private sector supporters of tropical disease research include foundations, pharmaceutical companies, volunteer agencies, and religious organizations. Private U.S. foundations have programs that have often served to highlight problems and identify opportunities not exploited by Federal agencies. The Rockefeller Foundation's Great Neglected Diseases program and the Edna McConnell Clark Foundation's focus on schistosomiasis are examples.

U.S. Funding of Tropical Disease Research

It is difficult to pin down a dollar figure that represents U.S. research in tropical diseases, because information is not standardized across agencies, and definitions of tropical diseases differ. **On the basis of analyses of information developed for this assessment, OTA estimates that, in recent years, the U.S. Government has annually contributed less than $100 million toward research in tropical diseases, out of a total annual biomedical research budget of well over $4 billion.** Contributions of private foundations are of lesser magnitude. Figures on tropical disease research funding by pharmaceutical companies are undocumented.

U.S. Department of Health and Human Services

NIAID's tropical medicine funding covers research in three general areas: 1) traditional tropical diseases (malaria, schistosomiasis, trypanosomiasis, leishmaniasis, filariasis, and leprosy); 2) general parasitology (cestodes, nematodes, trematodes, and protozoa); and 3) general tropical medicine (rickettsia, bacteriology, mycology, virology, and vector pathogens). In fiscal year 1983, NIAID funding for tropical medicine research was about $33 million, about 12 percent of NIAID's budget (less than 1 percent of the total NIH budget). About one-quarter of this funding supported researchers working at NIH (intramural research), and three-quarters went to researchers outside NIH (extramural research). In addition to the $33 million for tropical medicine research, NIAID spent approximately $3 million on projects in diarrheal diseases and ARIs (a large proportion of ARI funding is for influenza research, directed at domestic problems).

The Fogarty International Center of NIH does not have a tropical disease research program, but approximately $2 million annually is channeled through the Fogarty budget to the Gorgas Memorial Institute, for the operation of its laboratory in Panama. Fogarty also holds international confer-

ences and provides fellowships to foreign scientists, some of which contribute to the overall effort in tropical disease research.

CDC conducts tropical disease research primarily through the Center for Infectious Diseases and its Division of Parasitic Diseases. In fiscal year 1983, CDC spent an estimated $5 million on tropical disease research. This includes support of CDC's Medical Entomology Research and Training Unit in Guatemala.

U.S. Agency for International Development

Most AID funding for tropical disease research comes from the Office of Health. In fiscal year 1982, this amounted to about $14 million. About $5 million of this was the U.S. contribution to TDR, about $5.8 million was spent on research in malaria immunology and vaccine development, and $1.9 million was part of the core support for the International Center for Diarrheal Disease Research in Bangladesh. AID's Africa Bureau spent approximately $1.3 million on the biomedical research components of three projects: onchocerciasis control, combatting communicable childhood diseases, and schistosomiasis activities in Cameroon and the Sudan.

AID's Office of the Science Advisor supports additional research at the level of about $1 million in grants through the Program in Science and Technology Cooperation (PSTC) and through the National Research Council's Board on Science and Technology for International Development (BOSTID). Most of these funds go to researchers in developing countries.

U.S. Department of Defense

In fiscal year 1982, DOD spent about $13.5 million for biomedical research in tropical infectious diseases, representing about 6 percent of all DOD biomedical research funding. The Army and Navy conduct a certain amount of research themselves, as well as contracting out research both in the United States and in the tropics. The U.S. Army currently maintains the only large-scale antimalarial drug screening program in the world. It also maintains medical research units in eight developing countries, the largest such program of any U.S. Government agency.

U.S. Contributions to International Programs

The **Special Program for Research and Training in Tropical Diseases (TDR)**, administered by WHO, is cosponsored by WHO, the World Bank, and the U.N. Development Program. TDR was initiated in 1975 and has two main objectives: 1) to strengthen the biomedical research capabilities of the developing countries; and 2) to develop tools to control six tropical diseases (malaria, schistosomiasis, trypanosomiasis, leishmaniasis, filariasis, and leprosy).

By the end of 1981, TDR had received more than $95 million in contributions from 25 governments, other organizations, and the sponsoring agencies. The U.S. annual contribution to TDR was $4 million in 1980 and 1981 and just over $5 million in 1982.

WHO supports some tropical disease research in addition to its contributions to TDR. Under the general classification of communicable disease prevention and control, about $2.4 million of WHO funds went for research in tropical diseases during the 2-year period 1980-81.

WHO also supports two separate programs relevant to tropical diseases: one in ARIs and one in diarrheal diseases. Over the 2-year period 1980-81, WHO spent $381,000 for ARI research and just over $1 million for diarrheal disease research. WHO's 1982-83 diarrheal disease research budget was estimated to be about $3.8 million.

Precisely determining the U.S. contribution to WHO research programs is difficult, because funding for each set of projects comes both from the "regular budget" and from a spectrum of "extrabudgetary sources," in varying amounts. For the period 1980-81, the annual U.S. monetary contribution is estimated by OTA to be between $250,000 and $500,000.

Funding of U.S. Researchers in Tropical Diseases

Most of the tropical disease research funded by U.S. institutions is carried out by U.S. researchers. In fiscal year 1982, for example, NIAID awarded 96 percent of its tropical medicine funds to U.S. institutions and 4 percent to researchers in other industrialized countries. Often, however, investigations undertaken by U.S. institutions are carried out in close collaboration with institutions in less developed countries.

AID's Bureau of Science and Technology allocates almost 75 percent of its biomedical research funds to American institutions. Many of these institutions collaborate with organizations in the less developed countries. AID's Research Grants Program, administered by the Science Advisor's Office and by BOSTID (National Academy of Sciences), has so far allocated about 45 percent of its resources to American institutions, though the BOSTID portion of the program makes grants only to institutions in developing countries.

The DOD biomedical research program allocates about 75 percent of its extramural funds to organizations in the United States, 18 percent to institutions in less developed countries, and 5 percent to organizations in other industrialized countries.

The majority of biomedical research funds both of the Rockefeller Foundation (52 percent) and of the Edna McConnell Clark Foundation (77 percent) were awarded to American institutions.

U.S. researchers also receive funds from international organizations in excess of the U.S. contributions to such organizations' research budgets. In 1981, TDR awarded about one-third of its research funds to Americans, nearly equal to the U.S. contribution. The same year, WHO's program in diarrheal diseases awarded one-quarter of its research funds to American institutions, but the U.S. contribution represented 1 percent of the program's total budget.

OPTIONS

Development of Medical Technologies for Tropical Diseases

To encourage research and development of medical technologies for tropical diseases, Congress might consider the following options.

OPTION 1: Explicitly include drugs and vaccines for tropical diseases in the definition of "orphan drugs" under the Orphan Drug Act of 1983 (Public Law 97-414).

OPTION 2: Encourage Federal agencies, such as AID, to examine the possibility of interesting private companies in developing medical technologies for tropical diseases by guaranteeing purchases of products and assisting in field trials.

OPTION 3: Mandate the creation of and authorize funds for a quasi-governmental nonprofit corporation to undertake research and development of medical technologies for tropical diseases until the technologies become economically attractive enough for private industry to take over with the right to an exclusive license for the product.

OR

Stimulate the development of an international nonprofit corporation, funded through contributions from the U.S. Government, other governments, and international bodies, to undertake such research and development.

OR

Create a nonprofit corporation charged with ensuring the development and availability of prophylactic and therapeutic agents for use in developing countries for which there appears to be insufficient commercial interest.

Relatively few U.S. pharmaceutical companies are pursuing the development of drugs and vaccines for tropical diseases. The few that are often have entered the field because research for tropical parasitic diseases of humans is a spinoff of research on parasitic diseases of domestic agricultural animals. There is, at present, little financial incentive for pharmaceutical company activity in most human tropical diseases.

The lack of profitable markets for tropical disease pharmaceuticals does not correlate with a lack of patients, but with the high price of newly developed drugs (necessary to recoup research and development costs); the relatively small health budgets of developing country governments and the inability of most people in developing countries to pay for the drugs themselves; and unstable political conditions which make it risky for U.S. companies to rely on trade with specific developing countries.

The new medical products developed with biotechnology, largely vaccines and diagnostics, might provide a stimulus for activity by the pharmaceutical industry. With much of the developmental work on these products coming from publicly funded research, the research and development costs incurred by industry should be somewhat less. Much of the expense

of production, particularly for vaccines, however, is incurred in scaling up production and in clinical trials.

As the malaria vaccine now under development in the United States illustrates, there are also issues to be addressed in the commercialization of publicly funded research. Funding for the malaria vaccine's development has come from various U.S. Government agencies, private foundations, and WHO. WHO's policy is that the fruits of WHO research funding should be available to the world at large. This policy means that a commercial company desiring to produce the malaria vaccine, should it move to the production stage, would not be allowed to secure a patent. Because substantial costs are involved in developing a process for large-scale production of the vaccine, many companies would be unlikely to undertake the project without patent protection.

The Orphan Drug Act of 1983 charges the U.S. Government with the task of identifying and promoting "orphan products," defined as drugs and devices for rare diseases or conditions. The act defines rare diseases and conditions as ones that occur so infrequently that there is no reasonable expectation that the cost of development can be recouped by sales within the United States.

Four kinds of support for orphan drugs are authorized by the 1983 act:

1. A 50-percent tax credit on all clinical testing expenses associated with the drug.
2. Award of an exclusive 7-year right to market a drug that is unpatentable (through the Food and Drug Administration's new drug approval authority).
3. Technical assistance in the development of clinical testing protocols.
4. Award of grants and contracts for clinical testing expenses associated with an orphan drug.

In addition, public relations benefits may accrue to pharmaceutical companies developing orphan products.

Even with the incentives of the Orphan Drug Act, there is little reason to expect a major increase in the activities of U.S. pharmaceutical companies in tropical disease research. One alternative is some form of public funding expressly for pharmaceuticals for tropical diseases. Although setting up a nonprofit corporation is not the only means of injecting public funds into the process, there might be advantages to setting up a corporation, rather than simply adding money to TDR or increasing grants through NIH. The nonprofit corporation's research could be expressly aimed at eventual commercialization, and rules could be set up for the transfer of projects to for-profit pharmaceutical companies at the appropriate time.

Information for Congressional Decisions

OPTION 4: Hold a special appropriations hearing for tropical disease research with representatives from NIH, CDC, DOD, and AID, and perhaps invite international agencies and private foundations to participate.

AND/OR

OPTION 5: Require each agency mentioned above to submit a short report on the status of its tropical disease research, providing data specified by the Appropriations Committees for use during appropriations hearings.

Evaluating the adequacy of U.S. research efforts in the area of tropical diseases is difficult, because no specific goals have been enunciated except in the case of U.S. contributions to the TDR and WHO programs. By and large, each U.S. Government agency involved in funding or carrying out tropical disease research does so according to its own needs, and, in most cases, through legislation that passively allows tropical disease research activities rather than promotes them.

In the past, suggestions have been made to improve coordination among the Federal agencies involved with tropical disease research. Two very basic aims of such coordination would be: 1) to avoid duplication of effort, and 2) to identify gaps in the overall research agenda.

OTA found no evidence that the tropical disease research efforts supported by different Federal agencies are duplicative. The professional community in international health is relatively small and closeknit, and within that community, there is a high degree of awareness of the various activities taking place. Undetected duplication of effort is relatively unlikely also because the total amount of money spent on tropical disease research is small.

There do appear to be gaps in current tropical disease research activities, however, and some of them are identified in this assessment. It is possible that a coordinating committee of some sort, with representatives from the relevant agencies, could identify gaps and devise plans to fill them. However, the options cited above would allow the Appropriations Committees to see the range of related activities in tropical disease research and might serve as well as or better than a coordinating committee.

To obtain basic information comparable across Federal agencies, the Appropriations Committees could provide a framework for the presentation of information at hearings or in a report from agencies.

The following types of information might be included in the reports from U.S. Government agencies:

1. A summary of funded activities for each disease from a core list of tropical diseases (e.g., the diseases covered in this report). The information listed below might be required, including, where appropriate, indications of which research is strictly associated with tropical diseases and which only partially:
   —type of research—basic or technology-oriented;
   —if basic, category (immunologic, physiologic, etc.); and
   —if technology-oriented, category (preventive, diagnostic, therapeutic).
2. The same information as in (1) for other diseases at the discretion of each agency:
   —number of projects; and
   —total funding levels.

3. A rationale for the allocation of funds.
4. An indication of how much research is funded at institutions in the tropics, and how much in the United States, and acknowledgment of funded American researchers collaborating with researchers in the tropics.
5. An indication of U.S. contributions to international research efforts (principally WHO and TDR).
6. An assessment of gaps in research as perceived by the agencies.

Private foundations and international agencies funding tropical disease research could provide similar information about their activities and could provide additional perspective on research needs.

Research Funding

OPTION 6: Increase Federal funding for all aspects of tropical disease research.

OPTION 7: Amend the international health mandate of the U.S. Department of Health and Human Services (DHHS) to remove the limitations on the research DHHS may support in tropical diseases.

U.S. Government funding for tropical disease research in recent years has been less than $100 million annually, out of an annual Federal biomedical research budget of $4 to $5 billion. It is understandable that the disease problems of importance in the United States consume most of the resources, but there are perhaps a billion people in other countries suffering from or at risk for diseases which most U.S. citizens will never encounter.

Since the focus of this assessment has been tropical disease research itself, OTA has not identified specific funding programs or institutional bases for increases in funding. A National Academy of Sciences study now in progress is developing information that will be of direct value in formulating such programs and identifying the institutional resources that exist in this country. In the short term, however, it appears that the funding mechanisms that now exist could productively absorb funding increases.

Current authority for international health research within DHHS derives primarily from the International Health Research Act of 1960 (Public Law 86-610), the purpose of which is "to advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research and research training." The authority to undertake research for the good of people outside the United States rests with the President.

Congress could transfer the authority to make decisions about all aspects of tropical disease research to DHHS itself, the Department which includes NIH and CDC. It could do this by amending the language of the International Health Research Act to give DHHS the authority to "advance the status of the health sciences in the United States and thereby the health of *all* people."

Such a change would explicitly provide greater justification for DHHS research on diseases that are not major public health problems in the United States. Giving NIH, in particular, more flexibility to fund research on tropical diseases could stimulate the submission of a greater range of grant proposals and might provide the basis for additional contracts in the area of tropical diseases.

NOTE: Copies of the full report "Status of Biomedical Research and Related Technology for Tropical Diseases" can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, GPO stock No. 052-003-00987-1.

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